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Cont

71. (New) The method according to claim 69, wherein the primer pair is suitable for amplification by PCR or NASBA.

## REMARKS

Claim 15 has been amended. Claims 19-55 have been canceled and new claims 56-71 have been added. Therefore, claims 15-18 and 56-71 are currently pending.

The invention

Applicants have discovered a link between the existence of certain deletions in the BRCA1 gene and predisposition towards certain types of cancer. In particular, Applicants have demonstrated that deletions of exon 13 or of exon 22 of the BRCA1 gene are strongly linked to predisposition for breast and ovarian cancer.

Applicants' discovery is of major importance in improving the diagnosis of breast and ovarian cancer. Prior to the present invention, the link between deletions of exon 13/exon 22 of the BRCA1 gene and predisposition for breast and ovarian cancer was unknown.

Using this newly discovered information, Applicants have invented diagnostic test kits and hybridization probes useful for detecting these predispositions associated with deletions of stretches of nucleotides in the BRCA1 gene. The invention further includes methods for detecting deletions of exon 13 and exon 22 with these kits and probes.

The rejection under 35 U.S.C. §112, first paragraph

According to the Examiner, claims 15-55 define a compound solely by its functional utility, as a deletion, without any definition of the particular deletions claimed. Further the Examiner cites the revised guidelines for written description stating that a satisfactory disclosure of a "representative number" depends on whether one of skill would recognize that the Applicant "was in possession of the necessary common attributes or features of the

elements possessed by the members of the genus in view of the species disclosed." (Emphasis added).

The Examiner states that there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed, which comprise deletions of the BRCA1 gene in exon 13 or exon 22. Therefore, the Examiner concludes, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

In fact, since the entire nucleic acid sequence of the BRCA1 gene was known at the time of filing of the present application, the nucleotide sequences of deletions of exon 13 and 22 were entirely predictable. According to the U.S. Patent Office Guidelines on Written Description, even a description of a single example of a highly predictable genus is sufficient to adequately describe that genus.

The present claims 15-18 and new claims 56-71 recite diagnostic test kits, and methods for using means, such as primers and probes, capable of determining the presence in a sample of a deletion of exon 13 or of exon 22 of the BRCA1 gene. These primers and probes are complementary to sequences of the BRCA1 gene and are therefore entirely predictable on the basis of the known complete nucleic acid sequence of BRCA1. Thus, the common attributes or features shared by the primers and probes are the sequences complementary to the remaining BRCA1 gene sequence. Therefore, the complete genus of primer and probe sequences capable of determining the presence in a sample of a deletion of exon 13 or of exon 22 in the BRCA1 gene was predictable by one of ordinary skill given the present specification.

Addressing first the Examiner's allegation that the genus of probes for the detection of deletions of exon 13 and 22 are not adequately described: Applicants respectfully disagree. The specification discloses several actual working examples of primers and probes for the detection of deletions of exon 13 or of exon 22. See for instance the disclosure in

Examples 2 and 3, page 12 of the two sets of nested pairs of primers (SEQ ID NOS: 7 & 8 and 11 & 12; or SEQ ID NOS: 7 & 8 and 5 & 13) that are used to amplify the region including exons 12-24 for the detection of deletions in exon 13 or 22. See also, the disclosure in Example 4, at page 13, for a disclosure of the hybridization probe derived from PCR amplification of the exon 14-24 region using the primer pair of SEQ ID NOS: 18 & 19.

Addressing next the Examiner's allegation that the genus of deletions of exon 13 and exon 22 is not adequately described: Several deletions of exon 13 and exon 22 of the BRCA1 gene are fully described in the specification. See for example, the disclosed written description of the following deletions:

The deletion of 3885 nucleotides including exon 13 (nucleotide positions 44514-48348) disclosed at page 10, lines 33-36, and Figure 4.

The deletion of 172 nucleotides from exon 13 (nucleotide positions 46156- 46327) disclosed from the last line of page 10 to page 11, line 6.

The deletion of 510 nucleotides including exon 22 (nucleotide positions 79505-80014) disclosed at page 10, lines 27-30, and Figure 3.

The deletion of 74 nucleotides from exon 22 (nucleotide positions 79543-79616) disclosed at page 10, lines 30-32.

Therefore, a representative number of deletions of exon 13 and exon 22 are also described. Furthermore, the entire genus of deletions of exon 13 or of exon 22 of the BRCA1 gene was predictable by one of ordinary skill given the benefit of the disclosure of the present specification, as the full sequence of the BRCA1 gene was known at the time of filing of the application.

As to the Examiner's assertion that the claims are drawn to broad embodiments claimed by function for which no concomitant structure is provided: Applicants emphatically

disagree. As stated herein above, the entire sequence of the BRCA1 gene was known at the effective date of filing of the present application, along with the locations and sequences of the exons including exons 13 and 22. Therefore, the structures of all deletions of exons 13 and 22 were entirely predictable and adequately described by the present specification. Similarly, the structures of all possible probes for the detection of deletions of exon 13 and exon 22 were predictable from the known BRCA1 gene sequence and the present specification.

Therefore, Applicants respectfully assert that the genus of primers and probes for the detection of deletions of exons 13 and 22 is adequately described and the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

The rejection under 35 U.S.C. §112, second paragraph

At page 4 of the Detailed Action claims 15-55 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out an distinctly claim the subject matter which Applicant regards as the invention. The Examiner rejected claim 15 due to the use of the phrase "...means is provided for..." as failing to invoke the requirements of 35 U.S.C. §112, sixth paragraph. According to the Examiner, the citation to the specification at page 6, lines 3-15 is generic and would not support means plus function language.

Claim 15 has been amended to recite the standard "means for ..." language that invokes the statute at 35 U.S.C. §112, sixth paragraph. Applicants point out that the specification contains ample description of various means for detecting the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides in the BRCA1 gene, wherein the deletion comprises exon 13, or exon 22. Exemplified means include primers for amplification methods such as polymerase chain reaction (PCR) and nucleic acid sequence-based amplification (NASBA) and the like, at page 6, lines 28-29; probes for southern blotting at page 6, lines 30-31; probes for demonstrating

hybridization with a probe flanking both sides of a deletion, at page 6, lines 10-11; use of two probes (one on each side of a deletion) and primers for amplifying the stretch in between, at page 6, lines 12-13; probes for demonstrating lack of hybridization when using a probe hybridizing to a deleted sequence, at page 6, lines 13-15; and primer means for demonstrating lack of amplification between one or more sets of primers targeted at or near the deleted region, at page 6, lines 15-17.

Moreover, these means are further supported by the detailed description and the working Examples. For instance, Example 2 at page 12 describes the use of primer pairs of SEQ ID NOS: 7 and 8 for reverse transcription to obtain first strand cDNA for PCR of exons 12-24 and use of the obtained PCR products as templates for a second PCR of exons 12-24 using the nested primer pairs of SEQ ID NOS: 9 and 10.

Further, Example 3, at pages 12-13 describes the use of nested primer pairs of SEQ ID NOS: 11 and 12 for the second stage PCR using the same cDNA template as in Example 2 above. PCR of DNA carrying a deletion of 3835 base pairs, including exon 13 from genomic DNA using the primer pair of SEQ ID NOS: 5 and 13 is also described. Likewise, genomic PCR of DNA carrying a deletion of 512 base pairs spanning exon 22 using the primer pair of SEQ ID NOS: 14 and 15 is described in Example 3 at page 13.

Additionally, Example 4 at page 13 describes the use hybridization probes p11 and p1424 derived by PCR using primer pairs of SEQ ID NOS: 16 and 17, and 18 and 19 respectively. These hybridization probes were used for detection of exons 11 and 14-24 by southern blotting.

Applicants therefore assert that the means for detecting the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides in the BRCA1 gene, wherein the deletion comprises exon 13, or exon 22 are extensively exemplified and well described.

Applicants assert that claim 15 as amended properly invokes the "means plus function" requirements of 35 U.S.C. §112, sixth paragraph. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

The rejection under 35 U.S.C. §102(b)

At page 5 of the Detailed Action claims 15-45 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Miki et al. *Science* (1994) 266:66-71. The Examiner notes that the publicly available primers for every exon of BRCA1 cited at footnote 26 of the Miki et al. reference would inherently function in a diagnostic test to detect deletions, and large deletions of exons 13 and 22 in particular, because the resultant PCR products would differ in size from the PCR products of controls without the deletions. Also, the Examiner stated that the Miki et al. reference teaches the resultant PCR products would inherently function as hybridization probes for the detection of exons 13 and 22, and that such PCR products would comprise a sequence complementary to both sides of the deletion. Further, the Examiner noted that Miki et al. at page 69, figures 3 and 4, teach the elements necessary for southern and northern blotting.

In the first instance, the Examiner's citation to footnote 26 at page 71 of the Miki et al. reference does not comply with the requirements of public availability. Footnote 26 merely states that "Sequences of PCR primers used to amplify each exon of BRCA1 are available on request."

First and foremost, the statement in the footnote does not mean that the sequences are necessarily available to all. The authors are academic researchers who may be selective in making the sequences available to some but not all members of the public who request them. Nowhere in the Office Action of June 3, 2002 does the Examiner demonstrate that Miki, et al., in fact, made, or were willing to make, any sequences of PCR primers publicly available prior to the effective filing date of the present application.

Even if Miki, et al., made any sequences of PCR primers publicly available, and Applicants again emphatically repeat that the Examiner has not made out a convincing argument that they have, the Miki et al. reference, at most, simply discloses nucleotide sequences capable of acting as primers for amplifying each exon of BRCA1.

Claims 15 to 18 and claims 56 to 59, by contrast, recite a diagnostic test kit comprising a means for detecting a deletion in exon 13 or exon 22 of the BRCA1 gene. Miki, et al., do not disclose, and, in fact provide no motivation whatsoever to provide, such a test kit. Without the disclosure in the present specification of the Applicants' dramatic discovery that deletions of exon 13 or of exon 22 of the BRCA1 gene are strongly linked to predisposition for breast and ovarian cancer, there was no such motivation.

Similarly, claims 60 to 62 recite labeled probes for detecting a deletion in exon 13 or exon 22 of the BRCA1 gene.

The Miki et al. reference discloses nothing more than primers for each exon of the BRCA1 gene. There is no suggestion in Miki et al., to label the primers and to use them as probes in accordance with the claims.

Finally, claims 63 to 71 recite methods for detecting deletions in exon 13 or exon 22. As mentioned above, until the present Applicants discovered the link between deletions in exon 13 or exon 22 and a predisposition to breast and ovarian cancers, there was no disclosure or suggestion to detect such deletions.

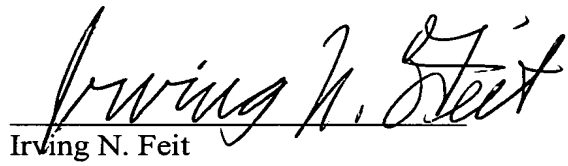
The Miki et al. reference discloses nothing more than primers for each exon of the BRCA1 gene. There is no suggestion in Miki, et al. to detect deletions of exon 13 and exon 22 as in the method of claims 63 to 71.

Therefore, the kits of claims 15-18 and 56-59, the labeled probes of claims 60-62 and method of claims 63 to 71 are neither specifically nor inherently disclosed, by the cited Miki et al. reference.

For all the above explained reasons, Applicants respectfully assert that the presently claimed subject matter is not anticipated by the disclosure of Miki et al. and consequently, the rejection under 35 U.S.C. §102(b) should be withdrawn.

If the Examiner has any questions relating to this Amendment or to this application in general, the Examiner is respectfully invited to contact the Applicants' attorney at the telephone number provided below.

Respectfully submitted,



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**VERSION OF AMENDMENT WITH**
**MARKINGS TO SHOW CHANGES MADE**

In the claims:

Please cancel claims 19-55 and add new claims 56-71 as follows (All the pending claims are recited for the Examiner's convenience):

15. (Amended) A diagnostic test kit for detecting [the presence of or] a predisposition for breast cancer, [wherein a means is provided for] comprising a means for detecting the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides in the BRCA1 gene [in a sample], wherein said deletion comprises [at least a major part of] exon 13 [and/or at least a major part of] or exon 22.

16. A diagnostic test kit according to claim 15, wherein the means comprises at least one probe for hybridization.

17. A diagnostic test kit according to claim 15, wherein the means comprises the necessary elements for Southern blotting.

18. A diagnostic test kit according to claim 16, wherein the probe comprises nucleic acid sequences complementary to both sides of the deletion.

56. (New) A diagnostic test kit according to claim 16, wherein the probe is labeled.

57. (New) A diagnostic test kit according to claim 15, wherein the means comprises at least one primer pair for amplification.

58. (New) A diagnostic test kit according to claim 15, wherein the means comprises at least two primer pairs for amplification, and wherein the two primer pairs comprise a nested set.

59. (New) A diagnostic test kit according to claim 57, wherein the primer pair is suitable for amplification by PCR or NASBA.

60. (New) A labeled probe for detecting a deletion of a stretch of nucleotides from a BRCA1 gene, wherein said deletion comprises exon 13 or exon 22.

61. (New) The labeled probe according to claim 60, wherein the probe comprises nucleic acid sequences complementary to both sides of the deletion.

62. (New) The labeled probe according to claim 61, wherein the probe comprises a nucleic acid sequence which is the product of a fusion between two ALU-elements in the BRCA1 gene.

63. (New) A method for determining the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides, wherein said deletion comprises exon 13 or exon 22; the method comprising:

(i) contacting said sample with at least one probe which alone or together with a means for detecting said deletion, distinguishes between a BRCA1 gene having said deletion and a BRCA1 gene not having said deletion, and

(ii) allowing hybridization between said probe and said nucleic acid to form a hybridization product, and

(iii) identifying the hybridization product.

64. (New) The method according to claim 63, wherein the probe is labeled.

65. (New) The method according to claim 63, wherein the probe comprises nucleic acid sequences complementary to both sides of the deletion.

66. (New) The method according to claim 63, wherein the nucleic acid derived from a BRCA1 gene is amplified.

67. (New) The method according to claim 66, wherein the probe comprises a nucleic acid sequence which is the product of a fusion between two ALU-elements in the BRCA1 gene.

68. (New) The method according to claim 63, wherein the hybridization product is quantified.

69. (New) A method for determining the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides, wherein said deletion comprises exon 13 or exon 22; the method comprising:

(i) contacting said sample with a primer pair which alone or together with a means for detecting said deletion, distinguishes between a BRCA1 gene having said deletion and a BRCA1 gene not having said deletion,

(ii) amplifying said sample to form an amplified product, and

(iii) identifying the amplified product.

70. (New) The method according to claim 69, further comprising contacting the amplified product with a second primer pair for amplification, and wherein the two primer pairs comprise a nested set.

71. (New) The method according to claim 69, wherein the primer pair is suitable for amplification by PCR or NASBA.